PATENT
Attorney Docket No.: MBM1200

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	J. Steeves and J. Dyer	Art Unit:	1646
Application No.:	09/530,234	Examiner	Chernyshev, Olga N.
Filed:	July 6, 2000		
Title:	IMMUNOLOGICAL COMPOSITIONS AND METHODS OF USE TO TRANSIENTLY ALTER MAMMALIAN CENTRAL NERVOUS SYSTEM MYELIN TO PROMOTE NEURONAL REGENERATION		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132 OF INVENTORS JOHN D. STEEVES AND JASON K. DYER

Sir/Madam:

As below-named inventors, we hereby declare that:

1. We are inventors of the subject matter which is claimed and for which a patent is sought on the invention entitled: "IMMUNOLOGICAL COMPOSITIONS AND METHODS OF USE TO TRANSIENTLY ALTER MAMMALIAN CENTRAL NERVOUS SYSTEM MYELIN TO PROMOTE NEURONAL REGENERATION," Application Serial No. 09/530,234 (hereinafter "the '234 application").

2. The attached *Curricula vitae* (Exhibits A1 and A2) delineate our educational and professional experience. Together we have experience in the fields of neuroscience, physiology and zoology. John Steeves holds a Ph.D. in neuroscience/physiology from the University of Manitoba and is currently a Professor of the Graduate Program in Neuroscience at the University of British Columbia. John Steeves also acts as Director of the International Collaboration on Repair Discoveries (iCord). Jason Dyer holds a Ph.D. in zoology from the University of Bristol, United Kingdom, and is currently on the Board Of Directors and is Chair of Scientific Advisory Board at Neuro Therapeutics Inc.

3. We have reviewed the Final Office Action mailed January 22, 2003 and we understand that the Examiner had alleged that the invention lacks enablement, as required by 35 U.S.C. §112. More specifically, the Examiner had rejected claims 46, 48 and 49 as allegedly lacking enablement for methods for promoting neuron repair or regeneration in a human subject by transient disruption of myelin or transient demyelination, comprising administering a therapeutically effective amount of the disclosed composition. We further understand that the

Examiner had alleged that the Applicant provides no information about the route and duration of administration, as well as the quantity and ratio of the composition to be administered.

4. Based on our experience in the field of neurobiology, we believe that the experiments provided in the patent application, such as Examples I, III and IV, demonstrating the ability of the disclosed compositions to promote neuron repair in a traumatized spinal cord rat model, are predictive of the ability of these compositions to promote neuron repair or regeneration in humans and that, provided with the examples and teaching of the '234 application, a skilled practitioner would be able to practice the invention as claimed without undue experimentation.

5. To demonstrate that non-human models, in particular rodent models, are accepted in the art as predictive of the efficacy of therapeutic methods for promoting neuron repair or regeneration in humans, we provide herewith as Exhibits B – E exemplary research/review articles taken from the scientific literature. These articles have undergone a rigorous peer review process by recognized experts in the field of neurobiology.

6. Exhibit B provides an overview of research in the field of spinal cord injury (SCI) repair and demonstrates that, in the field of neuronal research, rodent models (and in particular rat models) are used both to identify therapeutic treatments for human spinal cord injury repair and to support and predict the outcome of clinical studies based thereon. Exhibit B describes a number of therapies, including the drugs Neotrofin and Fampridine, that were developed in animal models and subsequently went on to clinical trials in humans. At page 1053, it is stated that animal models of SCI provide a good representation of the pathological processes involved in human spinal cord injuries.

7. Exhibit C1 presents results of experiments utilising a rat model of spinal cord demyelination to demonstrate that human olfactory ensheathing cells (OECs) are capable of remyelinating persistently demyelinated central nervous system (CNS) axons following transplantation into lesions in the rat spinal cord. At page 1587, the authors indicate that, based on these results, human OECs can be regarded as candidate cells for clinical trials in the treatment of traumatic and demyelinating diseases of the CNS.

8. A Phase I clinical trial using OECs is described in Exhibit C2. This clinical trial is being conducted at the Princess Alexandra Hospital in Brisbane, Australia under the clinical direction of Dr. Tim Geraghty and involves transplantation of OECs into the spinal cords of subjects with complete spinal cord injury. As indicated in Exhibit C2 at page 3, this trial was initiated based on results generated from rodent models.

9. Exhibit D describes experiments utilizing a rat experimental autoimmune encephalomyelitis (EAE) model to identify potential therapies for human neurodegenerative diseases. As outlined in Exhibit D, rats with EAE are a standard model for the evaluation of therapies for the treatment of Multiple Sclerosis (MS). As indicated in Exhibit D at page 3333, the drug Cop 1 (Copaxone) was first identified by its ability to suppress EAE in a number of animal species, including rat. Cop 1 is now a FDA-approved drug for the treatment of MS in humans and is administered by injection.

10. A number of drugs effective in spinal cord repair, spring-boarding from positive results based on animal studies, had gone on to advanced human clinical trials, prior to the filing date of the '234 application. For example, Copaxone had entered into Phase III clinical trials and Fampridine had entered into Phase II clinical trials. Accordingly, this is yet another basis to assert that a worker skilled in the art would have a reasonable expectation that efficacy demonstrated in rodent models of neurodegenerative disease is predictive of efficacy in humans, as of the date the '234 application was filed.

11. Exhibits E1 and E2 demonstrate a link between physiological processes involved in neurodegenerative disease and CNS injury. As discussed in these Exhibits, both CNS injury and neurodegenerative disorders result in inflammation, which can lead to secondary neurodegeneration. As a consequence of this common physiological response, treatments for CNS injury have potential application in the treatment of neurodegenerative diseases, and *vice versa*. For example, Exhibits E1 and E2 demonstrate that boosting the immune system by vaccination with synthetic peptides such as Cop 1 can both provide neuroprotection for the treatment of neurodegenerative disorders and suppress inflammation resulting from CNS injury.

12. Many of the experiments described in Exhibits E1 and E2 involve the use of rat models having crush-injured optic nerves or traumatised spinal cords. At page 618, Exhibit E1 describes the applicability of animal models of acute traumatic injury (such as spinal transection) to studies relating both to traumatic injury to the CNS and to chronic syndromes involving neuron degeneration (*i.e.* neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases). As outlined in both of these Exhibits, it is the identification of candidate drugs effective in treating animal disorders that leads to the clinical application of a therapeutic drug or vaccine.

13. In addition to the scientific research articles provided as Exhibits B – E, we are aware of a number of U.S. Patents that have issued with claims directed to methods of treating CNS related injuries or diseases that are supported by animal studies only. Two such patents are provided herewith as Exhibits F and G.

14. Claims 1 – 46 of Exhibit F are directed to methods of promoting axonal regeneration in an injured spinal cord of a mammal and to methods of promoting axonal regrowth after injury or disease that results in or is accompanied by axonal damage in the central nervous system (CNS) of a mammal. Claims 17 and 42 are specifically directed to methods of promoting axonal regeneration or regrowth in humans. Claims 1 – 46 are supported in their entirety by studies performed solely on rodents, in particular, mice and rats, as set forth at columns 12-21 of the patent. Axon regeneration was investigated using a transected optic nerve rat model.

15. Claims 1 – 26 of Exhibit G are directed to methods of promoting axonal regeneration in the central nervous system (CNS) of a mammal comprising administering an effective amount of allogeneic mononuclear phagocytes into the CNS of a mammal at or near a site of injury or disease of the CNS that results in or is accompanied by axonal damage. Claims 22 and 24 are directed specifically to methods of promoting axonal regeneration in humans. Again, these claims are supported in their entirety by studies performed solely on rodents, as set forth at columns 10-14 of the patent. Axon regeneration was investigated using a transected optic nerve rat model.

16. As is demonstrated by the exemplary references and patents described above, one skilled in the art would appreciate that efficacy in treating rat models of CNS injury and disease correlates with a reasonable expectation of efficacy in humans. The Exhibits provide numerous examples of where therapeutic drugs or vaccines having clinical applications were predicted through effective treatment of an animal disorder/dysfunction. Accordingly, the methods for promoting neuron repair or regeneration in a human subject using the composition disclosed in the '234 application would be considered by those skilled in the field of neurobiology to be supported by the results provided in the application that utilise a standardized system, *i.e.* the rodent model.

17. Furthermore, the skilled technician appreciates that the usual method of determining effective doses of any new drug or therapeutic is through clinical trials. The development of a new drug follows a well documented and routine sequence of steps for which strict procedures and guidelines have been set out by various regulatory agencies. An initial safe starting dose for human trials is usually established through pre-clinical studies conducted in animals. Phase I clinical trials conducted in human volunteers are specifically designed to determine, amongst other parameters, safe levels of the drug for human administration, drug tolerance and the best route of administration for a new drug. These procedures are fundamental to the drug development process. Accordingly, a practitioner in the field would understand that the dose, duration and route of administration for the compositions disclosed in the '234 application could be determined through routine clinical trials, as is standard in the clinical sciences without undue experimentation.

18. Finally, it is our understanding that it is not necessary for an Applicant to specify the dosage or method of use for an invention if it is known to one skilled in the art that such information could be obtained without undue experimentation (MPEP 2164.01(c)). As indicated above, a skilled technician could readily determine appropriate dosages and modes of administration for the claimed compositions through routine clinical trials without undue experimentation. The MPEP also indicates that considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled and that testing for full safety and effectiveness is best left to the FDA (MPEP 2164.05).

19. We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: March 9, 2004

John D. Steeves

Dated: March 10, 2004

Jason K. Dyer